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Randomized Trial in the Phillipines

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## INTRODUCTION

In 1990 breast cancer accounted for 837,000 new cases per year (WHO World Health Report 1997), and it was the most frequent cancer in women. Incidence rates are still rising in many countries, particularly in the developing world (Coleman and Estève, 1993). It seems that these trends are likely to continue, since the current pattern of later childbearing, decreasing fertility, and 'westernization' of diets will all be associated with increased risk.

At present, our knowledge of environmental risk factors does not permit formulation of any practical primary prevention programs. The introduction of adjuvant therapy with Tamoxifen has improved survival of older cases and a decline of mortality from breast cancer below age 50, observed in some high-risk countries, has also been attributed to adjuvant therapy (Nab *et al.*, 1994, Olivotto *et al.*, 1994). However, further improvements in surgical techniques, or in radiotherapy, are very unlikely to provide more than marginal changes in mortality rates.

A much greater decrease in deaths from breast cancer is achievable through screening programs which lead to detection of cancers which are smaller, at an earlier stage, and less malignant than those which surface clinically. Several randomized trials of screening for breast cancer have been carried out; in the majority the screening modality used was mammography, with or without physical examination of the breasts. There is a clear consensus that such screening programs are capable of decreasing the risk of mortality from breast cancer in women aged 50 or older (Miller *et al.*, 1990; Day, 1991; Moss, 1996). The efficacy of mammography in women below 50 is still a very controversial issue resulting in contradictory recommendations and policies (Moss, 1996; Nelson, 1997). At best, mortality reduction in this age group would be only 15% or one-half that of older women (based on meta-analyses of randomized trials). The reason of lower efficiency of mammography in younger women is not clear; possible causes are cancers growing faster in these ages or sensitivity of mammography in the pre-menopausal breast being relatively low.

Population screening programs which depend upon mammography require extensive provision of expensive technology and highly trained radiologists and radiographers. The cost per life-year saved is therefore relatively high (Barnum and Greenberg, 1991), and clearly an inappropriate use of health care resources for many countries (WHO, 1984).

The alternative screening strategies which have been proposed are physical examination of the breasts (PE), and breast self-examination (BSE). Short-term results of a large scale trial of BSE among 300,000 textile workers in Shanghai, China, conducted by researchers of the University of Washington have been recently published (Thomas *et al.*, 1997). Biases such as low compliance with the intervention, failure of proper randomization or low proficiency in performing BSE could be confidently excluded. No significant reduction of breast cancer mortality in the intervention group has been detected after 5 years of follow-up and the distribution of stage at diagnosis in screen and control groups were very similar. As discussed by the Authors, both results are not definitive; even in trials of mammography a reduction of mortality appeared only after 5 years from entry into the study and stage at diagnosis, which is assessed retrospectively, may well be affected by a rate of mis-classification which can obscure existing differences in the intervention and control groups.

Nevertheless, the small size of the lesions diagnosed in the control subjects in this trial (47 %  $\leftrightarrow$  2 cm diameter) suggests a high level of health-awareness in the Shanghai population, and may give little scope for improvement in outcome through early detection by BSE.

At present PE has never been used as the sole modality of screening, so that its effectiveness is not known. Indirect evidence based on estimates of the accuracy of PE relative to mammography suggests that this type of examination could reduce mortality rates by 2/3 to 3/4 of that achievable by mammography screening in women aged 50 or more. PE alone may be effective in younger women, among whom up to 25% cancers are missed by mammography; in addition, there is evidence that PE improves the performance of mammography. The working group who reviewed in 1979 the results of the Breast Cancer Detection Demonstration Project, the first large non-experimental evaluation of mammography, stated that high priority should be given to the evaluation of PE as a single screening modality. The recommendation was not followed by action until the project described here, possibly because of the rapid spreading of mammography in most developed countries which vitiated the feasibility of an unscreened control group.

The purpose of the present work was to establish 1) whether a program of mass screening by PE performed by trained paramedical personnel could be set up in a developing country as part of the routine activity of first level

health services, and 2) whether and to what extent such a program could reduce mortality from breast cancer. The location is Metro Manila and Rizal Province of the Philippines. This population has a relatively high incidence of breast cancer, considerably above that of other Asian populations, and comparable to that in southern Europe.

## **BODY**

The study is a randomized controlled trial of the effect of annual physical examination (PE) of the breasts performed by trained nurses/midwives, in reducing mortality from breast cancer. The study area comprises the central, more urbanized municipalities of the National Capital Region (Districts I, II, III and IV), which includes 12 municipalities each having municipal health centers in the township area and barangay health stations in more rural areas. In 1990, the estimated size of the female population aged 35-64 was about 340,000. The units of randomization are health centers (HCs) within the selected municipalities of the Manila - Rizal area.

Women aged 35-64 years resident in the intervention HC areas were offered annual breast examinations, carried out by specialized midwives/nurses. At the first visit, these women were also instructed in the technique of breast self-examination (BSE) and provided with a leaflet in the local language explaining the purpose and methodology of BSE.

Women in the control area received no active intervention, but were exposed to the general health education campaigns carried out by municipal authorities and voluntary bodies.

The examiners were trained using a program already developed and tested in the Philippines, making use of breast silicon models. Training was repeated for selected groups of examiners with detection rates markedly above or below the mean. Women eligible for screening were invited to participate through a variety of mechanisms but mainly by home visits.

At the first visit women were interviewed to record demographic variables and risk factors for breast cancer. Instruction in BSE was given and PE performed. Demographic characteristics of women who refused PE were also recorded.

Women with detected abnormalities were referred for final diagnosis to special clinics, made available in 3 major hospitals staffed by project personnel.

After one year of intervention, compliance with referral was only 21% and all remedies put in place to improve it (see below), did not significantly affect the proportion of positive women who reached a definitive diagnosis.

The intervention was therefore discontinued after the completion of the first round and follow-up of the intervention and control cohorts has been undertaken.

## **Results**

### **A) Intervention**

During 1995 a coordinating center was set up. Two hundred and two Health Centers were randomized to intervention and control arms. Hospital clinics for referral of positive women and mechanisms for documentation of results were established.

Personnel from the intervention HCs were recruited and trained. It soon became evident that the regular personnel of HCs could not reach the scheduled rate of 14,000 woman-examinations per month. Therefore, nurses were recruited to work full-time for the project (FTNs). In March 1996, the intervention reached a regular pace. The first round of the intervention was completed in December 1997. The results of the intervention after completion of the single round of examinations, are summarized in table 1. Three-thousand four hundred and ninety two women were detected positive for a lump at first examination. Of these, 42.3% actively refused further investigation, 21.8% who did not report to the tumor clinics had moved away or died when visited at home and seventy-one cases (2%) are waiting for final diagnosis. Only 32% (1,110 women) completed the diagnostic process, of these 33 were malignant cancers detected.

### **Comparison of characteristics of compliers and refusers.**

In the annual report of 1997 we presented an analysis of the characteristics of a sample of women who accepted PE and of those who refused it. The two groups do not differ by age, prevalence of smoking or compliance with screening for cervix cancer, the latter being an indication of general attitude towards preventive practices. In contrast with what is observed in western countries, refusers are of higher social class, as indicated by greater average income and significantly lower parity.

**B) Action taken to improve compliance with clinical investigation among women detected positive.**

One thousand women who were positive for a lump at the initial visit but who had not subsequently turned up at a referral clinic were visited a second time to assess the motives for non-compliance. The survey indicates that the main reasons for non-compliance are inconvenience and costs. In order to induce greater motivation to seek medical attention, medical teams formed by a doctor and a nurse and equipped to perform needle biopsies, were sent to visit non-compliers at home in order to obtain a final diagnosis. This activity commenced in March 1997 (recruitment and training of doctors) and was completed by end of April 1998. The results of active clinical follow up are summarized in table 2.

**Modification of study protocol and plan of work**

The experience of the first 2 years of field activity indicates that a screening program by PE can attain high coverage in this urban population. The positivity rate (3.0%) is sufficiently low to make this type of intervention cost-effective provided that the positive predictive value and sensitivity of the test prove to be high. At present, the positive predictive value of the screening test appears rather low but a definitive value will be available only when all incident cases will be identified and linked to the cohort. Sensitivity will be estimated eventually by comparing the incidence of interval cancers (not detected by screening) in the intervention group, with the incidence in the control group. The cancer registries will provide these data.

The potential of the intervention is obviously compromised by the very low rate of compliance with referral of women detected positive at PE. This is far too low to have any impact on the risk of dying from breast cancer in the intervention group. The low compliance rate was the main problem shown by the pilot study conducted in 1990-1991; the reason for this was identified in the cost of transport and diagnostic examinations which most women could not afford. Therefore, provision to reimburse diagnostic expenses was made in the project protocol. It appears that this mechanism is not sufficient to compensate for loss of working-days. The project have therefore brought the diagnostic facilities to positive women in the hope that the relatively few who result positive for malignant cancer would have a strong motivation to seek medical care. Unfortunately this remedy improved compliance with clinical investigation only by 9%, with the cost of treatment and cultural barriers remaining the main obstacles to further clinical investigation.

In 1997 it was clear that the program as a whole would not be able to reduce mortality from breast cancer in this population. The reason for this is the low compliance with clinical investigation and treatment of women found positive at PE. Moreover, all remedies put in place to overcome, at least, logistical problems linked to referral failed to improve the compliance. A better understanding of the cultural determinants of the attitude of this population towards health practices would help the Department of Health in developing future strategies.

**Revision of study protocol.**

In October 1997 we submitted a revision of the study protocol which was accepted by the US Army Medical Research Command. The revision of the study concerns essentially discontinuation of the intervention after completion of the first round and undertaking of follow up of the target population. This will provide information on the effectiveness of the prevalent screen (incidence and mortality rates in the two groups), as well as identifying the risk factors for breast and other female cancers in this population. No analytical study has ever been conducted to explain the relatively high incidence of breast cancer in this population. The information collected by interview at time of the intervention will allow us to quantify the excess incidence attributable to known risk factors.

The cohorts (intervention and control) will be followed for up to 10 years to study the onset of breast cancer and resulting mortality in relation to screening. The association between reproductive factors and cancer of the breast has never been studied in a prospective study of this size in a population with fertility rates characteristic of developing countries but showing patterns of cancer risk quite high for Asian standards. Other cancer sites, which will be related to reproductive factors, tobacco smoking, alcohol consumption and family history of cancer are cervix, ovary, corpus uteri, colon, lung, kidney and gallbladder. Table 3 shows the number of cases expected in the next 5 to 20 years in the cohort interviewed, by cancer site. Cancers of the kidney and



gallbladder have been associated with parity in women however, being rather rare cancer sites the association has been investigated only in small studies.

#### Data management and follow-up, January-September 1998.

Procedures to computerize the data collected have been established and regular data entry ensured the maintenance of data bases of women examined, women detected positive and final diagnoses. Data entered are subject to systematic checks for errors of coding and typing and for inconsistencies in the information recorded. The population lists have also been computerized.

A software program was developed in Lyon for the purpose of identifying records pertaining to the same woman. The program makes use of the usual basic demographic items - names and surname, date of birth, age and detailed address - and allows for differences in spelling or variations in the reported date of birth. Each variable contributing to the matching process is assigned a weight, which summarizes its discriminating power and the likelihood that it is reported incorrectly. The resulting matching score allows linkage of records within the same file (e.g. two screens of the same woman) or in different files.

The master file of the cohort of women examined at least once is being matched with the list of the population resident in the intervention areas in May 1997. This process will output a cohort of unexamined women who were eligible for examination who either refused it or were not reached by the intervention. The comparison of breast cancer incidence in screened and unscreened subgroups of the intervention cohort will provide an indication of the effect of selection bias.

Procedures in the two cancer registries serving the study populations (Manila-PCS and Rizal-DOH) have been improved, so that general case finding is taking place in a more timely manner than previously. Additional staff have been recruited and trained to trace cases and report data by means of new abstract forms which include extensive information on extent of disease (tumor size, spread and nodal involvement). Table 4 summarizes the clinical characteristics of the incident cases recorded up to July 1997. The recorded incidence is still rather incomplete for years 1996-97. About 50% are already at stage III-IV at diagnosis (out of those whose stage is known) and over 88% of these tumor are of size greater than 2 cm..

In summary, the following files have been created and are being maintained:

1. Master file of women examined. It provides identification of the women, data on risk factors obtained by interview and outcome of physical examination. Data entry completed in June 1998.
2. File of women positive for a lump and referred for further clinical investigation. Contains all information on diagnostic procedures performed and their outcome. Completed in June 1998.
3. Nominal lists of the population resident in the intervention and control areas in May 1997. Data entry is complete, checks for duplicates is ongoing.
4. File of the outcome of first and second screen-examinations for a sample of over 5,000 women who were screened twice. It is being updated with the results of the second examination.
5. File of all incident breast cancer cases in the target population. Updated regularly with the new cases detected by the cancer registries.
6. File of death certificates mentioning cancer. Periodically updated.

Record linkage between these files is being performed:

1. Matching of the master file of screened women with the lists of the population to identify the actual cohort of unscreened women.
2. Matching of breast cancer cases recorded by the cancer registries with the cohort of examined women and population lists, to identify incident cases in the screened cohort and interval cases.
3. Matching of the breast cancer file with death certificates mentioning cancer.
4. Matching of deaths certificates mentioning breast cancer with the population lists of both intervention and control areas.

Follow-up to assess vital status of intervention and control cohorts.

The efficiency of different means to assess vital status of the women belonging to the study cohorts is being tested. A questionnaire will be mailed to a sample of 500 women to assess response rates. The sample is stratified by age and health center to account for differences in the socio-economical level of the women. Contacts by telephone will also be attempted.

The feasibility of computer-assisted manual matching of all death certificates, irrespective of the cause of death, with the file of the study cohorts is also being assessed.

The first systematic update of vital status is planned for year 2000.

Control cohort

The file of the control cohort has been completed and computerised by combining the population lists compiled manually in 1996 and the electoral lists for the control areas; only women present on both files have been included. A random sample of 1000 women has been drawn from the resulting list to be traced and interviewed by the same questionnaire adopted for the intervention. This will take place in January - February 1999. The purpose of this sample survey is to estimate the actual proportion of the control cohort that is present in early 1999, and to compare the characteristics of this cohort with those of the intervention group as a check on the randomization procedure. If randomization was successful women in the control cohort will show the same pattern of risk factors.

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Table 1.  
Results of the single round screening, completed in December 1997.

<b>Intervention</b>			
No. interviewed and examined	147,558		
<b>Women detected positive</b>			
Number of women detected positive and referred to tumor clinics	3,492		
positivity rate:		2.4%	
No. referred who completed the diagnostic process:	1,110		
percent compliance (includes women visited at home):		31.8%	
of which, No. referred who did not attend clinic and were visited at home (see text and table 4)	631		
No. with final diagnosis among women visited at home:	585	93.7%	
Outcome of diagnoses (3,492 women):			
no mass	545	15.6%	
malignant breast cancer:	33	0.9%	
benign breast disease:	532	15.2%	
actively refused further investigation (at clinics or home visits):	1,476	42.3%	
attended other clinic:	73	2.1%	
pending diagnoses:	71	2.0%	
not traced at initial address or died:	762	21.8%	

Table 2.  
Pathology outcome of screen-detected lumps in referral clinics and after home fine needle biopsy (FNB).

	referral clinics	%	home visits and FNB	%	total	%
total evaluated:	<b>497</b>		<b>631</b>		<b>1128</b>	
no mass	286	57.6	259	41	545	48.3
unsatisfactory biopsy	1	0.2	46	7.3	47	4.2
benign disease	188	37.8	315	49.9	503	44.6
malignant	22	4.4	11	1.7	33	2.9

Table 3

Expected number of cases in the intervention cohort, by follow-up and cancer site.

	follow-up	
	5 years	10 years
Colon	77	187
Rectum	56	130
Gallbladder	16	38
Lung	154	387
Breast	676	1,484
Cervix uteri	321	700
Corpus uteri	85	195
Ovary etc.	133	297
Kidney	26	60
Thyroid	109	232

Table 4  
Clinical characteristics of Breast Cancer Cases diagnosed in Metro Manila  
(study area - intervention and control) in 1995-1997 (provisional)

## A) Stage

year of incidence	O-I	II	III-IV	all staged	unstaged	Total
1995 - No.	4	141	144	289	220	509
%	1.4	48.8	49.8	100.0	43.2	
1996 - No.	1	80	79	160	156	316
%	0.6	50.0	49.4	100.0	49.4	
1997 - No.	-	13	19	32	109	141
%	-	40.6	59.4	100.0	77.3	
Total	5	234	242	481	485	966

## B) Size

	<i>in situ</i>	<2.0 cm.	2.0 - 5.0	> 5.0cm.	Extension to chest wall or skin	all staged
1995	5	38	148	90	49	330
%	1.5	11.5	44.8	27.3	14.8	100.0
1996	2	23	96	58	35	214
%	0.9	10.7	44.9	27.1	16.4	100.0
1997	-	4	32	13	15	64
%	-	6.3	50.0	20.3	23.4	100.0
Total	7	65	276	161	99	608
%	1.2	10.7	45.4	26.5	16.3	100.